ORIGINAL ARTICLE

A Crossover Trial of Hospital-Wide Lactated Ringer's Solution versus Normal Saline

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ABSTRACT

BACKGROUND

Whether lactated Ringer's solution is clinically superior to normal saline for routine intravenous administration of fluids is uncertain.

METHODS

In an open-label, two-period, two-sequence, cross-sectional, cluster-randomized, crossover trial, we assigned hospitals in Ontario, Canada, to use either lactated Ringer's solution or normal saline hospital-wide for a period of 12 weeks. After a washout period, hospitals switched to the other fluid for 12 weeks. The primary outcome was a composite of death or readmission to the hospital within 90 days after the index admission. Secondary outcomes were the individual components of the primary outcome, as well as the length of stay in the hospital, initiation of dialysis within 90 days after the index admission, a visit to the emergency department within 90 days, and discharge to a facility other than home. Data on outcomes were obtained from health administrative databases. The analyses were conducted at the hospital level, and the primary estimand was the effect of the use of lactated Ringer's solution as compared with normal saline averaged across all participating hospitals.

RESULTS

Seven hospitals completed both 12-week periods before the trial was interrupted owing to the coronavirus disease 2019 pandemic. Data on the primary outcome were available for 43,626 eligible patients. The mean (±SD) incidence of the composite of death or readmission to the hospital within 90 days after the index admission was 20.3±3.5% with lactated Ringer's solution and 21.4±3.3% with normal saline (adjusted difference, −0.53 percentage points; 95% confidence interval, −1.85 to 0.79; P=0.35). Results for all secondary outcomes were consistent with those for the primary outcome. No serious adverse events were reported.

CONCLUSIONS

A hospital-wide policy to administer lactated Ringer's solution rather than normal saline did not result in a significantly lower incidence of death or readmission to the hospital within 90 days after the index admission. (Funded by the Canadian Institutes of Health Research and the Ottawa Hospital Academic Medical Organization; FLUID ClinicalTrials.gov number, NCT04512950.)

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SHOUT
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Crystalloid fluids, including normal saline and lactated Ringer's solution, are among the most common interventions used in the treatment of hospitalized patients to reestablish hemodynamic stability, replace fluid losses, or maintain intravascular volume.[1,2] Normal saline and lactated Ringer's solution have been used for several decades. Lactated Ringer's solution and other balanced crystalloid fluids contain less chloride than saline and reduce the risk of hyperchloremic acidosis.[3] Only recently has the safety of crystalloid fluids been compared in large, randomized trials. A single-center, multiple-crossover trial involving noncritically ill patients in the emergency department found that balanced crystalloid fluids were associated with a lower incidence of major adverse kidney events at 30 days than normal saline.[2] A systematic review of 13 randomized, controlled trials comparing balanced crystalloids with normal saline in a total of 35,884 critically ill participants showed no significant difference in mortality (17.4% with balanced crystalloids and 18.2% with saline; relative risk, 0.96; 95% confidence interval [CI], 0.91 to 1.01) or in the incidence of the use of renal replacement therapy (5.6% and 6.0%, respectively; relative risk, 0.95; 95% CI, 0.81 to 1.11) in trials with a low risk of bias.[4] However, the investigators in that analysis and those in another patient-level meta-analysis involving a Bayesian approach concluded that there is a high probability that balanced crystalloids are associated with lower in-hospital mortality and a lower incidence of the use of renal replacement therapy than normal saline.[5]

Several randomized, controlled trials have compared balanced crystalloid fluids with normal saline with respect to clinical outcomes among patients in the emergency department and intensive care unit (ICU).[2,6-13] To address a gap in evidence regarding the effects of balanced crystalloid solutions on patient outcomes outside these settings, we designed the FLUID trial.[14] The primary objective of the trial was to compare lactated Ringer's solution with normal saline as the main crystalloid fluid used hospital-wide from the time of hospital admission to discharge with respect to the incidence of death or readmission to the hospital within 90 days after the index admission.

Methods

Trial Design and Oversight

We conducted this investigator-initiated, open-label, pragmatic, two-period, two-sequence, cross-sectional, cluster-randomized, crossover trial at seven academic and community hospitals in Ontario, Canada. Patients were not recruited on an individual basis; all clinical data were obtained from health administrative sources housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences), which is an independent, nonprofit research institute with a legal status that allows for the collection and analysis of health care and demographic data under the provincial health information privacy law. Each participating hospital was defined as a cluster and assigned to one of two sequences (lactated Ringer's solution followed by normal saline or normal saline followed by lactated Ringer's solution). A cluster-randomized design was chosen because the intervention was implemented hospital-wide; a crossover design was chosen to improve the power and statistical efficiency of the trial. Reporting of the trial was guided by the Consolidated Standards of Reporting Trials (CONSORT) extension for cluster-randomized, crossover trials.[15]

Lactated Ringer's solution or normal saline (the control) was used according to a hospital-wide policy, and a site-tailored strategy for comprehensive education and communication was targeted to all physicians and nurses.[16] The trial included two 15-week periods. In each period, week 1 served as a run-in, and during weeks 2 through 13 (a period of 12 weeks), all patients with an index admission to the trial hospital were eligible for analysis. Weeks 14 and 15 were the washout period, during which the trial fluid remained stocked in the hospital for use by patients admitted during weeks 2 through 13; however, new patients admitted during weeks 14 and 15 were not included in the analysis. The risks of carryover were minimized by considering index hospitalizations only and incorporating a washout period to allow most patients admitted during the first period to be discharged before the crossover occurred (Fig. 1).

The Ottawa Methods Centre coordinated the trial, which was overseen by the FLUID executive and steering committees in collaboration with the

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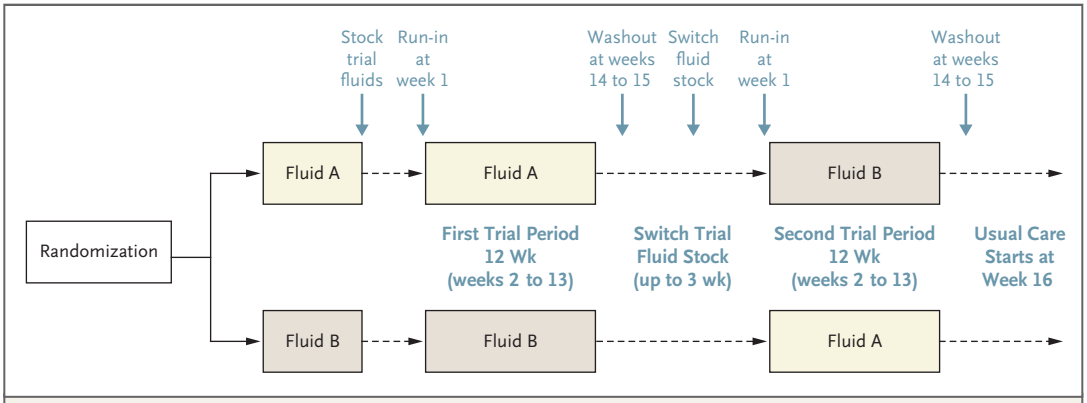
Stock trial fluids
Run-in at week 1
Washout at weeks 14 to 15
Switch fluid stock
Run-in at week 1
Washout at weeks 14 to 15
Randomization
Fluid A
Fluid A
Fluid B
Fluid B
Fluid B
Fluid A
First Trial Period 12 Wk (weeks 2 to 13)
Switch Trial Fluid Stock (up to 3 wk)
Second Trial Period 12 Wk (weeks 2 to 13)
Usual Care Starts at Week 16

Figure 1. Trial Design.

The trial included two active 12-week periods. Before each period, we allotted time (1 to 3 weeks) for participating sites to stock the assigned trial fluid throughout the hospital, after which there was a 1-week run-in period to give hospital staff (physicians and nurses) time to familiarize themselves with trial operations and the automatic substitution order; no patients were included in the analysis during the 1-week run-in period. The run-in period was followed by a 12-week active trial period (weeks 2 through 13); all patients with an index hospital admission during this time were included in the analysis unless they met criteria for exclusion. Each 12-week active trial period was followed by a washout period lasting either 1 week (sites 1 through 5) or 2 weeks (sites 6 and 7) to ensure that patients who were admitted close to the end of the active trial period received the same trial fluid throughout their hospital stay; no patients admitted during the washout periods were included in the analysis.

Canadian Critical Care Trials Group. The Canadian Institutes of Health Research and the Ottawa Hospital Academic Medical Organization funded the trial. Baxter Healthcare ensured that sufficient amounts of the trial fluid were available at participating hospitals. Neither the sponsors nor Baxter Healthcare had input into the design or conduct of the trial, the analysis or interpretation of the data, or the writing of the manuscript.

The protocol (available with the full text of this article at NEJM.org) was approved by the Ottawa Health Science Network Research Ethics Board for Clinical Trials Ontario and by the ethics board at each participating institution. A waiver of patient consent was approved because the intervention was implemented hospital-wide and posed minimal risk to patients.[17] The protocol and statistical analysis plan were published previously.[14] The first and last authors designed the trial with input from coauthors, and ICES gathered data. An author employed by ICES conducted analyses. The first author wrote the initial draft of the manuscript, and all the coauthors contributed to manuscript revisions and agreed to submit the manuscript for publication. The first and last authors and the author who conducted analyses vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The original design was changed to permit trial sites to begin the intervention at different times (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

ELIGIBILITY CRITERIA FOR PATIENTS AND HOSPITALS

Hospitals were eligible for the trial if they admitted at least 1500 patients during each trial period and had level II or III ICU capacity.[18] All patients with an index admission during the trial period were eligible for inclusion, regardless of exposure to the trial fluid (information about the exposure of individual patients to the trial fluid was not available in the health administrative database), if they did not meet any criteria for exclusion. An index admission was defined as a patient's first admission with no prior hospital admission in the previous 90 days. Key exclusion criteria were an age younger than 1 month, a missing birth date, admission that did not meet the definition of an index admission, and admission during the run-in or washout period.

RANDOMIZATION AND INTERVENTION

Hospitals underwent sequential, unrestricted randomization. The randomization sequence was

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computer generated by an independent statistician at the central coordinating site with the use of a permuted block design with a block size of two. The randomization sequence was maintained on a password-protected computer and was revealed to site investigators approximately 1 month before the first trial period was initiated at their site.

During each trial period, hospital staff ensured that the assigned trial fluid accounted for at least 80% of the inventory of crystalloid fluids on each ward at all times (with the nonassigned fluid accounting for ≤20%). For sites with electronic order entry, an automatic substitution order for the assigned trial fluid was initiated each time the treating clinician ordered either normal saline or lactated Ringer's solution. Bedside nurses implemented an automatic substitution order at sites with manual order entry. Physicians could exclude patients from use of the trial fluid if there were clinical concerns about exposure to the fluid; such patients were nevertheless included in the analyses. To monitor adherence, the logistic services reports at each hospital tracked the inventory of lactated Ringer's solution and normal saline on all clinical shelves throughout the hospital daily.

OUTCOMES

The primary outcome was a composite of death or readmission to the hospital within 90 days after the index admission (data on both types of events were validated with >99% accuracy in the ICES system).[19,20] Mortality data were obtained with the use of the Registered Persons Database, and data on hospital readmission were obtained from the Discharge Abstract Database. Secondary outcomes were death within 90 days after the index admission, hospital readmission within 90 days, length of stay in the hospital, initiation of dialysis within 90 days after the index admission, a visit to the emergency department within 90 days, and discharge to a facility other than home. Data on all secondary outcomes were obtained from the Discharge Abstract Database and the National Ambulatory Care Reporting System. Because exposure to the intervention at the individual patient level was unknown and the primary objective of the trial was to inform a decision at the health-systems level, the primary estimand was the average treatment effect among clusters (i.e., the effect of the intervention for an average hospital, referred to as the cluster average).[21] Thus, data on all outcomes were obtained at the individual patient level but were aggregated to the hospital level.

SAFETY

Participating hospitals monitored serious adverse events by means of routinely scheduled safety committee meetings or morbidity and mortality rounds. Principal investigators at each site reported any serious adverse event related to the administration of trial fluids to the central coordinating site.

DATA SOURCES AND DATA MANAGEMENT

All clinical data were obtained from population-based health administrative databases at ICES (see Section 1 of the Supplementary Appendix). The datasets were linked with the use of unique encoded identifiers and analyzed at ICES. Definitions of each baseline variable and all outcome measures are provided in the data dictionary in Section 2 of the Supplementary Appendix.

DESCRIPTIVE ANALYSES

Baseline data were collected and summarized as means and standard deviations for continuous variables or counts and percentages for categorical variables. Outcome data were summarized as percentages within individual hospitals and trial periods and presented as unweighted means and standard deviations. Overall adherence was calculated as the total use of the assigned trial fluid divided by the total combined use of lactated Ringer's solution and normal saline according to the hospital inventory system.

STATISTICAL ANALYSIS

We calculated that a sample size of 12 sites in a cluster-randomized, crossover design would provide the trial with 80% power to detect an absolute difference of 1 percentage point in the primary outcome at a two-sided significance level of 0.05, assuming an incidence of primary-outcome events of 16% with normal saline and 15% with lactated Ringer's solution, a within-period intracluster correlation coefficient of 0.006, a cluster autocorrelation coefficient of 0.95, and an average of 1500 patient admissions per hospital per month.[22] These estimates were calculated from available data that had been routinely collected from January 1 to December 31, 2013, from all eligible hospitals across the province of Ontario.

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The target difference of 1 percentage point was discussed among the members of the FLUID executive committee and was considered by the Canadian Critical Care Trials Group to be highly relevant at the population level from a hospital and health care system perspective. Our calculations accounted for nonadherence on the basis of data from a pilot trial[23] in which the level of adherence was 80% with lactated Ringer's solution and 94% with normal saline. We added 2 sites to the target sample size as an approximate correction[24] and a further 2 to account for variation in the size of hospitals,[24] for a final sample-size calculation of 16 sites. We estimated that a total of 16 hospital sites would yield data on approximately 144,000 hospital admissions. Although the target sample size was set at 16 hospitals, the trial was stopped after 7 hospitals had completed the trial owing to the infeasibility of conducting the trial during the coronavirus disease 2019 (Covid-19) pandemic.

All analyses were performed independently at ICES. As specified by the statistical analysis plan,[14] analyses were conducted according to the intention-to-treat principle, and all eligible admitted patients were included regardless of actual exposure to the trial fluid. A two-sided P value of less than 0.05 was considered to indicate statistical significance for the primary outcome. Because no multiplicity corrections were specified for secondary outcomes, statistical significance was not reported for secondary outcomes. The widths of confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

Primary and secondary outcomes were summarized at the level of the individual hospital and trial period and analyzed with the use of linear regression with trial period, intervention, and hospital as independent variables, as recommended for cluster-randomized, crossover trials with small numbers of clusters.[21,24,25] Equal weight was given to each hospital to obtain unbiased estimates for the cluster-average treatment effect.[26] We adjusted for the prespecified patient covariates of age, sex, case-mix group (defined according to Canadian Institute for Health Information grouping methods on the basis of diagnosis, intervention, length of stay, and resource use), Elixhauser Comorbidity Index score, and ICU admission within 1 day after hospital admission with the use of the two-stage method of Hayes and Moulton (see Section 1 of the Supplementary Appendix).[27] The t distribution with degrees of freedom equal to the number of clusters minus 2 was used. The primary analysis modeled trial period as a binary variable (first or second). Additional analyses were conducted to account for sequential trial initiation by modeling calendar time as a continuous variable with the use of both a restricted cubic spline and a simple linear term.

The primary outcome was also analyzed within prespecified subgroups that generally involved patients with greater-than-anticipated exposure to the trial fluid, a higher risk of death than the overall population, or adverse outcomes. Subgroups were defined according to variables including age (<18 years, 18 to ≤65 years, 66 to ≤80 years, or >80 years), sex, admission for surgery (elective, urgent, or emergency), comorbidities as defined by Elixhauser et al.,[28] Elixhauser Comorbidity Index score (with higher scores indicating a greater burden of diseases associated with an increased risk of in-hospital death) and score quartiles,[29] ICU admission, infection, infection with ICU admission, infection with organ dysfunction, infection with organ dysfunction and ICU admission, trauma with an injury severity score of 12 or higher (scores range from 0 to 75, with higher scores indicating greater severity), trauma with an injury severity score of 12 or higher and ICU admission, traumatic brain injury, and traumatic brain injury with ICU admission. These analyses were conducted as described for the primary analysis but with stratification according to subgroup variables and without covariate adjustment, and results were presented with the use of forest plots.

Sensitivity analyses for the primary outcome excluded some populations: patients who had vaginal and cesarean births, patients admitted for elective surgery, patients admitted for psychiatric reasons, and patients who may have been exposed to both types of trial fluids (those admitted during the first trial period and discharged during or after the second trial period or the second-period washout, and patients admitted during the second trial period and discharged after the washout period). Missing data for each outcome were summarized according to treatment group. Mean imputation within hospitals was used for missing baseline covariates. The statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

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RESULTS

PATIENTS

The trial was conducted between August 2016 and March 2020. From seven participating hospitals, a total of 43,626 patients (22,017 in the group receiving lactated Ringer's solution and 21,609 in the group receiving normal saline) were included (Fig. 2). No data were missing with respect to the primary outcome or any of the secondary outcomes.

Baseline characteristics of the patients were generally similar in the two trial groups (Table 1 and Table S1). Adherence to the use of the assigned trial fluid was 78.2% with lactated Ringer's solution and 93.6% with normal saline (Fig. S2).

OUTCOMES

At 90 days after the index admission, the mean (±SD) incidence of death or readmission to the hospital was 20.3±3.5% with lactated Ringer's solution and 21.4±3.3% with normal saline, with a cluster-level adjusted absolute difference in risk of −0.53 percentage points (95% CI, −1.85 to 0.79;

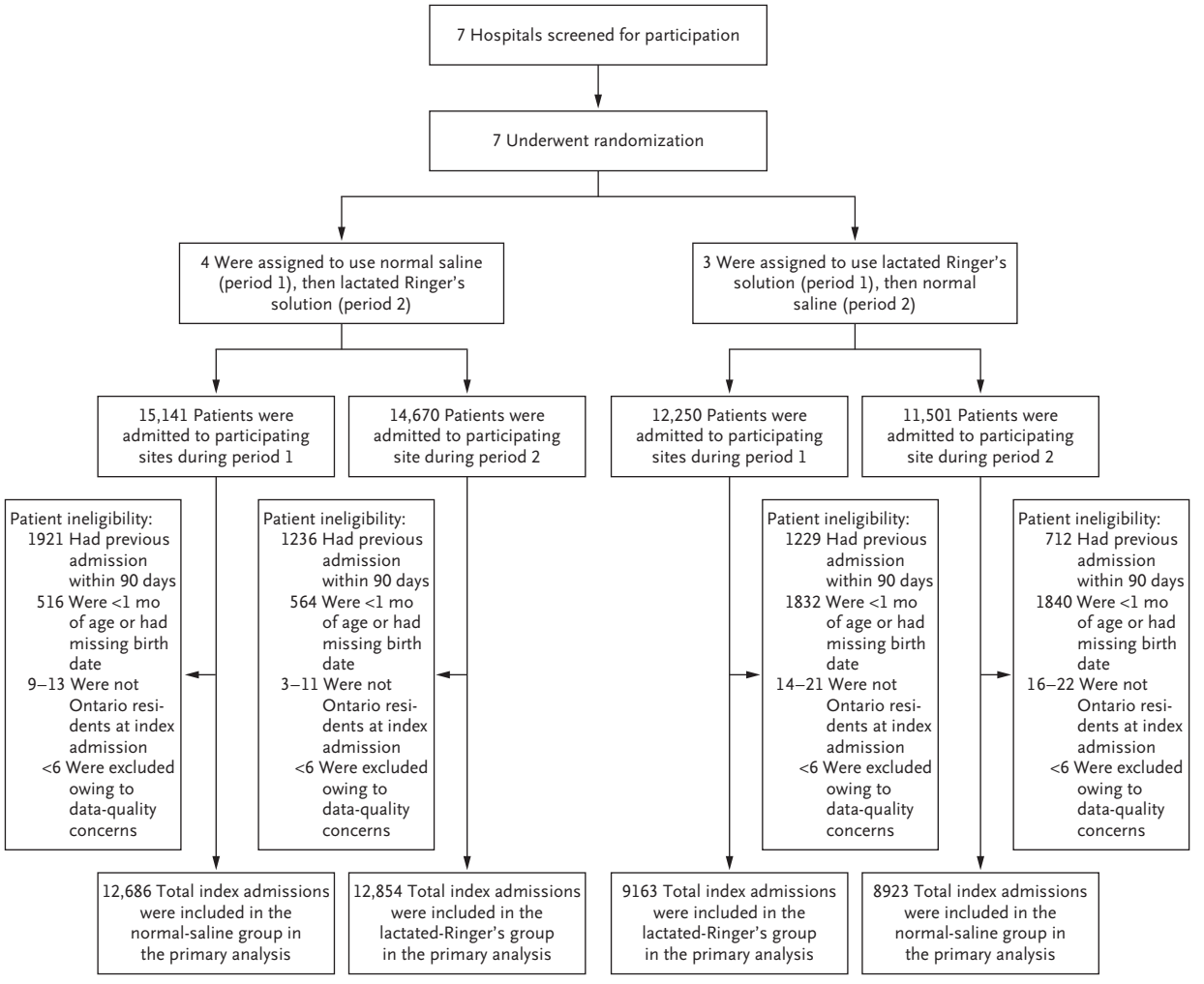
7 Hospitals screened for participation
7 Underwent randomization
4 Were assigned to use normal saline (period 1), then lactated Ringer's solution (period 2)
3 Were assigned to use lactated Ringer's solution (period 1), then normal saline (period 2)
15,141 Patients were admitted to participating sites during period 1
14,670 Patients were admitted to participating site during period 2
12,250 Patients were admitted to participating sites during period 1
11,501 Patients were admitted to participating site during period 2
Patient ineligibility: 1921 Had previous admission within 90 days 516 Were <1 mo of age or had missing birth date 9–13 Were not Ontario residents at index admission <6 Were excluded owing to data-quality concerns
Patient ineligibility: 1236 Had previous admission within 90 days 564 Were <1 mo of age or had missing birth date 3–11 Were not Ontario residents at index admission <6 Were excluded owing to data-quality concerns
Patient ineligibility: 1229 Had previous admission within 90 days 1832 Were <1 mo of age or had missing birth date 14–21 Were not Ontario residents at index admission <6 Were excluded owing to data-quality concerns
Patient ineligibility: 712 Had previous admission within 90 days 1840 Were <1 mo of age or had missing birth date 16–22 Were not Ontario residents at index admission <6 Were excluded owing to data-quality concerns
12,686 Total index admissions were included in the normal-saline group in the primary analysis
12,854 Total index admissions were included in the lactated-Ringer's group in the primary analysis
9163 Total index admissions were included in the lactated-Ringer's group in the primary analysis
8923 Total index admissions were included in the normal-saline group in the primary analysis

Figure 2. Screening, Randomization, and Analysis.

Where ranges are given, exact values are suppressed owing to data privacy or a data sharing agreement between ICES and data providers. In the case of patients excluded owing to data-quality concerns, the validity of the date of death is unclear because the database indicates that the date of death occurred before the index admission. These patients were excluded from analyses according to standard ICES procedures.

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Lactated Ringer's Solution (N=22,017)	Normal Saline (N=21,609)
Age — yr	58.5±20.6	58.7±20.8
Female sex — no. (%)	12,682 (57.6)	12,623 (58.4)
Place of residence — no (%)†		
Rural	2,221 (10.1)	2,092 (9.7)
Urban	19,743 (89.7)	19,471 (90.1)
Unknown	53 (0.2)	46 (0.2)
Income quintile — no. (%)‡		
1	4,874 (22.1)	4,828 (22.3)
2	4,549 (20.7)	4,574 (21.2)
3	4,362 (19.8)	4,267 (19.7)
4	4,066 (18.5)	4,094 (18.9)
5	4,087 (18.6)	3,778 (17.5)
Unknown	79 (0.4)	68 (0.3)
Case-mix group — no. (%)§		
Medicine	8,787 (39.9)	9,011 (41.7)
Surgery	9,379 (42.6)	8,804 (40.7)
Pregnancy and childbirth	3,706 (16.8)	3,670 (17.0)
Mental health	145 (0.7)	124 (0.6)
Elixhauser Comorbidity Index score¶		
Mean	2.6±5.2	2.8±5.3
Median (IQR)	0 (0–5)	0 (0–5)
Elixhauser Comorbidity Index quartile‖		
1	1,399 (6.4)	1,185 (5.5)
2	12,671 (57.6)	12,482 (57.8)
3	2,219 (10.1)	2,090 (9.7)
4	5,728 (26.0)	5,852 (27.1)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Place of residence was determined by Statistics Canada with the use of census metropolitan area (CMA) or census agglomeration (CA) data.
‡ Income quintiles were determined on the basis of income data for the nearest Canadian census-based neighborhood within a CMA or CA. Lower numbers indicate lower incomes.
§ Case-mix groups were defined according to Canadian Institute for Health Information methods that use similarities in diagnoses, interventions, length of stay, and resource use to stratify patients receiving acute care in an inpatient setting.
¶ The Elixhauser Comorbidity Index is a composite score that weights individual coexisting conditions (referred to as comorbidities) according to their independent associations with mortality. The composite score can be negative or positive because some of the conditions are inversely associated with mortality. Scores range from –19 to 89, with higher scores indicating a greater burden of diseases associated with an increased risk of in-hospital death.
‖ Higher numbers indicate higher scores on the Elixhauser Comorbidity Index.

P=0.35) and a cluster-level adjusted relative risk of 0.97 (95% CI, 0.90 to 1.05; P=0.35) (Table 2). The estimated within-period intracluster correlation coefficient was 0.0064, and the cluster autocorrelation coefficient was 1. Additional analyses accounting for a continuous period effect (calendar time) showed results consistent with those of the primary analysis (Table S2).

The secondary outcomes are presented in Table 2. Results of the prespecified subgroup analyses are shown in Figure 3 and Figure S3. The exclusion of patients who were admitted for ob-

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Table 2. Summary of Cluster-Level Analyses of Primary and Secondary Outcomes.*

Outcome	Lactated Ringer's Solution (N=7)	Normal Saline (N=7)	Adjusted Mean Difference (95% CI)†	Adjusted Relative Difference (95% CI)
Primary outcome				
Composite of death or readmission within 90 days after index admission (%)	20.3±3.5	21.4±3.3	−0.53 (−1.85 to 0.79)‡	0.97 (0.90 to 1.05)
Secondary outcomes				
Death within 90 days after index admission (%)	6.9±1.2	7.6±1.7	−0.26 (−0.95 to 0.43)	0.97 (0.89 to 1.07)
Readmission to hospital within 90 days after index admission (%)	15.1±2.9	15.4±2.1	−0.06 (−1.78 to 1.67)	0.99 (0.87 to 1.11)
Emergency department visit within 90 days after index admission (%)§	21.2±3.1	21.0±2.3	0.28 (−2.51 to 3.06)	1.01 (0.88 to 1.15)
Initiation of dialysis within 90 days after index admission (%)	0.5±0.3	0.6±0.5	−0.12 (−0.34 to 0.11)	0.99 (0.56 to 1.77)
Hospital length of stay (hr)	164.7±34.7	172.3±34.2	−0.002 (−0.006 to 0.002)	NA¶
Discharge to a facility other than home (%)	15.4±4.8	16.2±4.6	−0.49 (−1.59 to 0.62)	0.96 (0.90 to 1.03)

* Percentages are the incidence of primary- and secondary-outcome events averaged across seven hospitals (clusters). Hospital length of stay is also averaged across hospitals. Plus–minus values are means ±SD. CI denotes confidence interval.
† Values are from linear regression analysis of cluster-level summary data adjusted for age, sex, case-mix group, Elixhauser Comorbidity Index score, and admission to the intensive care unit within 1 day after hospital admission. All analyses account for a binary effect of trial period (first or second) and clustering according to hospital. Values are expressed as percentage points, except in the case of hospital length of stay, in which the adjusted mean difference is expressed in hours.
‡ P=0.35.
§ Numbers include only the first visit to an emergency department within 90 days after the index admission.
¶ The adjusted relative difference is not applicable (NA) for hospital length of stay because length of stay is a continuous outcome.

stetrical, elective surgical, or psychiatric conditions and those who may have been exposed to both types of trial fluids did not change the estimate of effect (Table S3). Participating sites reported no serious adverse events to the central coordinating site.

DISCUSSION

This hospital-wide, cluster-randomized, crossover trial of lactated Ringer's solution as compared with normal saline did not show a significant difference in the incidence of a composite of death or hospital readmission within 90 days (the primary outcome). Meta-analyses of subgroups from randomized, controlled trials involving critically ill patients suggest potential benefit from the use of balanced crystalloid fluids in cases of sepsis[4,5] but harm in cases of traumatic brain injury.[5] In the present trial, the subgroups of patients with sepsis (437 patients) and traumatic brain injury (90 patients) were small in proportion to the patient population as a whole, and results for these groups were consistent with the overall findings of the trial.

Strengths of this trial include a diverse and representative population of patients with heterogeneous diagnoses who were admitted to seven different hospitals. The administration of trial fluids occurred in emergency departments, hospital wards, step-down units, operating rooms, pre- and postoperative assessment units, and ICUs. Patients received the assigned trial fluid from hospital admission through discharge to reduce contamination with the alternate trial fluid. With more than 43,000 patients from both academic and community centers involved, this trial is one of the largest randomized trials to compare lactated Ringer's solution with normal saline. These features enhance the generalizability of the findings.

A limitation of this trial was the inability to recruit the total of 16 hospitals as originally planned owing to the Covid-19 pandemic. Hence, the trial had less power to detect differences that were small — but important to patients — at the level of the hospital or health care system. Adherence to the use of lactated Ringer's solution as measured by the inventory system of each hospital was marginally lower than adherence to

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Subgroup	No. of Patients	Lactated Ringer's Solution	Normal Saline	Risk Difference (95% CI)
		estimated incidence		*percentage points*
Sex				
Female	25,305	18.2±3.9	19.4±4.6	−1.11 (−2.49 to 0.28)
Male	18,321	23.7±3.2	25.0±3.2	−1.25 (−2.98 to 0.48)
Age				
1 mo to 18 yr	198	8.7±4.8	10.4±10.3	−1.74 (−12.4 to 8.92)
>18 to 65 yr	24,650	14.1±4.4	14.6±3.7	−0.43 (−1.75 to 0.89)
>65 to 80 yr	11,693	24.9±4.5	25.0±5.8	−0.08 (−2.92 to 2.76)
>80 yr	7,085	34.9±1.7	38.3±2.5	−3.41 (−6.25 to −0.56)
Case-mix group				
Medicine	17,798	31.4±4.8	32.7±3.9	−1.23 (−3.80 to 1.34)
Mental health	269	14.5±6.3	16.9±9.3	−3.48 (−12.9 to 5.96)
Pregnancy and childbirth	7,376	7.1±3.2	12.5±16.9	−0.50 (−2.13 to 1.13)
Surgery	18,183	14.9±3.7	15.2±3.9	−0.21 (−1.58 to 1.17)
Elixhauser quartile				
1	2,584	14.7±5.6	15.1±5.4	−0.18 (−3.23 to 2.87)
2	25,153	13.3±2.8	13.8±2.9	−0.40 (−1.21 to 0.40)
3	4,309	27.3±2.9	27.3±3.1	0.35 (−2.77 to 3.47)
4	11,580	36.0±4.4	38.2±5.0	−2.43 (−4.89 to 0.04)
ICU within 1 day				
No	39,254	19.6±3.7	20.4±3.3	−0.76 (−1.84 to 0.33)
Yes	4,372	31.6±6.8	35.1±7.0	−3.45 (−7.80 to 0.90)
Type of surgery				
Emergency	627	7.1±10.1	8.3±3.6	−1.22 (−9.59 to 7.15)
Urgent	1,008	13.0±2.1	11.4±3.8	1.76 (−2.46 to 5.98)
Elective	11,484	12.3±4.4	12.3±4.6	0.14 (−1.61 to 1.88)

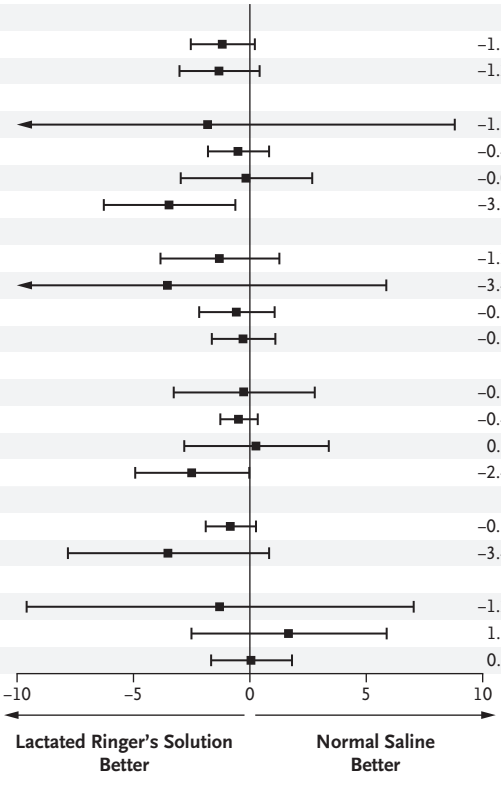

Figure 3. Subgroup Analyses.

Forest plots present results of the prespecified subgroup analyses of the primary outcome, a composite of death or hospital readmission within 90 days after the index hospital admission. Estimates are expressed as the mean (±SD) incidence of primary-outcome events across hospitals. Analyses were conducted with the use of stratified linear regression at the hospital level with trial period, assigned trial fluid, and hospital as independent variables. Case-mix groups were defined according to Canadian Institute for Health Information grouping methods on the basis of diagnosis, intervention, length of stay, and resource use. Elixhauser quartiles are based on scores on the Elixhauser Comorbidity Index, with higher scores indicating a higher number of coexisting conditions. ICU within 1 day denotes admission to the intensive care unit within 1 day after hospital admission.

the use of normal saline. Health administrative data as compared with data collected in other trials by research coordinators may be less accurate and prone to misclassification bias. However, misclassification in our trial would have been nondifferential. Owing to the complex implementation of this hospital-wide intervention, each hospital began the trial at a different time, an approach that rendered the trial vulnerable to potential confounding due to seasonal effects. However, estimates of treatment effect were consistent with the main findings when secondary analyses were adjusted for calendar time.

This trial adds to the growing body of evidence about the influence of crystalloid fluids on patient outcomes. Our findings align with those of recent meta-analyses of randomized, controlled trials that suggest a small but clinically relevant reduction in mortality with balanced crystalloids as compared with normal saline. As noted, however, our ability to assess small differences was limited by Covid-19–related restrictions on recruitment. Small differences could have major effects at the level of the hospital or health care system.

In this cluster-randomized, crossover trial involving a heterogenous group of patients in academic and community hospitals, the use of lactated Ringer's solution as compared with normal saline did not result in a significant difference

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in the incidence of death or readmission to the hospital within 90 days.

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This article is dedicated to the memory of Christopher Parish.

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